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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/155,590	09/30/1998	JEFFREY SCHLOM	2026-4230US1	8846

7590 07/29/2004

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/155,590	SCHLOM ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-15,25,27,32-34,66-68,70 and 71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-15,25,27,32-34,66-68,70 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Please note that the examiner assigned to this application has changed.

2. Sections of the text of Title 35 US Code not found in this action can be found in a prior action.

3. Claims 10-15, 25, 27, 32-34, 66-68 and 70 have been amended. Claim 71 has been added. Claims 10-15, 25, 27, 32-34, 66-68, 70 and 71 are pending and under consideration.

4. After review and reconsideration, the species election requirement of May 23, 2000 is withdrawn.

5. Claims 10-15, 25, 27, 32-34, 66-68, 70 and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is vague and indefinite in the recitation of a "mutant ras peptide comprising an amino acid sequence of at least 8 to no more than 13 amino acids", because a peptide "comprising" is open language and not limited in the length of the amino acid sequence. Further, claim 10 is vague and indefinite because of the further recitation of the motif "Xaa1 Leu Xaa2 Val Val Gly Ala Xaa3 Gly Val". In order to fulfill the specific embodiment of the motif, a given amino acid sequence would require all the amino acids of the motif, and therefore be of a minimal length of 10 amino acids. Thus, there is a conflict between the clause reciting the amino acid motif and the clause reciting "at least 8...amino acids" because it would not be possible to have an amino acid sequence which minimally comprises either 8 or 9 amino acids, which would satisfy the specific embodiment of the recited motif.

6. The rejection of claims 10-15, 25, 27, 32-34, 66-68, 70 under 112, first paragraph for the reasons set forth on page 7, section 7 of the previous Office action. Applicants attempted at amending the claim to limit the length of the amino acid sequence has not overcome this rejection. Newly added claim 71 is also rejected for the same reasons of record.

Further, the specification is not enabling for how to use said peptides comprising the instant motif in cancer immunotherapy as contemplated on page 2, lines 29-31. The instant claims are drawn to peptide comprising the motif of Xaa1 Leu Xaa2 Val Val Gly Ala Xaa3 Gly Val. This motif is known to encompass amino acids encoded by codons 5-14 of Ki-Ras with Xaa1 corresponding to the residue encoded by codon 5, Xaa2 corresponding to the residue encoded by codon 7 and Xaa3 corresponding to the residue encoded by codon 12 (Fossum, International Journal of Cancer, 1994, Vol. 56, pp. 40-45, see Table 1). The claims are drawn to encompass variant amino acids of D, V, C, A, R or S at position Xaa3 which is encoded by codon 12 which are recognized in the art as a hot spot for point mutation in the K-ras gene (Thiede et al, Nucleic Acids Research, 1996, Vol. 24, pp. 983-984, especially Figure 2 and Gedde-Dahl, European Journal of Immunology, 1993, Vol. 23, pp. 754-760, page 754, first column, lines 4-9). It is noted that the art does not teach that the K-ras gene exhibts mutational hot spots at codons 5 or 7, not does the art teach tumors exhibiting altered K-ras at codons 5 or 7. Neither the specification, nor any art of record provides evidence supporting the presence of mutant K-ras peptides altered by substitution of tyrosine for the wild type lysine at the residue encoded by codon 5, or altered by the substitution of any amino acid in place of the wild type v alanine in the residue encoded by codon 7. Claim 10 further comprises the limitation that said peptide elicits a peptide specific human CD8+ CTL immune response. However, if a patient had a cancer expressing an altered K-ras gene, it would not be expected that the altered K-ras peptide would encompass the variant peptides encoded by codons 5 and 7 as encompassed by the claims, because there is no evidence of such K-ras mutations in tumor specimens. It is known in the art that CD+8 T cells recognize the linear sequence of a specific peptide of about 8-10 amino acids when presented in the context of MHC Class I receptor. Abrams et al (European Journal of Immunology, 1996, Feb, Vol. 26, pp. 435-443) teach that the efficiency of an anti-tumor CTL response and the extent of its biological relevance in vivo requires T cell receptor recognition of tumor-derived endogenous antigen in the context of MHC class I (page 440, first column, lines 3-6 under section 3.4). It would be expected that a 8-10-mer peptide harboring a single alteration in the amino acid sequence recognized by a given CD+8 T-cell clone would not recognize a variant peptide presented in the MHC class I receptor as the recognition is based solely on amino acid sequence rather than conformation as in the case of an antibody. Thus, without evidence

that the mutations encompassed by the ras peptides of the instant claims were present on human tumor cells, one of skill in the art would not expect the CD+8 T cells elicited thereby to induce lysis of tumor cells in vitro.

The specification teaches the vaccination of patients with the mutated ras antigens and the isolation of CD+8 T cells specific for the vaccinated peptides from said individuals (page 13, lines 22-35). However, the specification is not enabling for how to use the instant peptides to induce an immune response in vivo which would constitute an anti-cancer immuotherapy for the following reasons:

The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). The specification has provided evidence that a T-cell clone generated against a K-Ras peptide is able to lyse transfected cells expressing the transduced peptide in vitro. Paul teaches that lymphocytes, which includes CTL, from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1

peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 tumor peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion"). In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. These references serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105) and the abstract of Algarra et al (International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of specific CD+8 T cells upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, the abstract of Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules because they are lacking MHC expression.

Paul (ibid) states that the induction of tolerance is a mechanism by which tumor cells escape immune detection. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that clonal deletions of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete or shed antigens. Thus, the presence of a rapidly growing tumor can overwhelm the immune system and result in the death of immature T-cells which would be reactive to the claimed peptides.

Further, the generation of CTL which can lyse target cells in vitro has no apparent nexus with anti-tumor cytolytic activity in vivo. Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing proteins expressed in tumors can be isolated from patients, but that the existence of said T-cells in said patients does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the lysis of target cells expressing mutated ras peptides in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo.

Paul (ibid) teaches tumor cell escape mechanisms which include rapid growth as a means to overwhelm a slower immune response, (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor

Immunity" and Table 4) and deficient antigen processing by tumor cells The art teaches that the presence of a small number of tumor cells or the presence of a large number of tumor cells gives rise to tolerance (Paul, page 1166, second column, lines 19-23 under the heading "Sneaking Through"). Based on this observation, it is reasonable to conclude that a small number of slow growing tumor cells would elicit tolerance, and a large number of rapidly growing tumor cells would also elicit tolerance in line with the bi-phasic response reported by Paul. Thus, it appears that the interaction of the tumor cells with the host can produce tolerance by means of clonal deletion within the thymus of said host. Furthermore, the relationships between the multitude of different tumor cells exhibiting said mutated Ras peptide would be variable as different types of organs and different histological types of neoplasms can harbor the disclosed Ras peptides. Fossum et al (ibid) teach the presence of T-cell reactivity in a patient which was specific for a mutation introducing D in place of G at position 13, although no evidence of said mutation was found within the tumor of said patient. Fossum et al conclude that said patient had eliminated the cells with the mutation due to the generation of a CD+4 and a CD+8 response to said mutated peptide. It is noted that said patient had not eliminated tumor burden as a result of the putative CD+4 CD+8 immune response against the specific mutated Ras peptide because the formalin fixed tumor was assayed for the presence of said peptide. One of skill in the art would reasonably conclude based on what is known about tumor heterogeneity, that the assay of the tumor sample did not provide a comprehensive assay for all the tumor tissue within said patient. Further, Fossum et al (International Journal of Cancer, 1994, Vol. 56, 40-45) teach that the failure of the immune system of said patient to eliminate the tumor cells may be due to an escape of a subset of tumor cells not harboring said mutation which serves to corroborate the teachings of Paul regarding tumor escape mechanisms. Fossum et al suggest that the T-cell response in vivo may be initiated and boosted by injection of the antigen in immunogenic form. However, if the tumor cells do not express said antigen, or have reduced expression of said antigen, it would not be expected that said tumor cells would be eliminated by CD+8 T cell specific for said antigen.

It is noted that Abrahms et al (ibid) teach the ras3-15(V12) and ras5-14(V12) peptides which are within the scope of the instant claims (Table 1) with the exception of the limitation "wherein when Xaa2 is valine, Xaa1 is tyrosine" because the ras3-15(V12) and ras5-14(V12)

peptides have valine at Xaa2 but have a lysine at Xaa1. Abrahms et al suggest that the presence of a tyrosine at position 1 may serve as an anchor for the peptide to the MHC I receptor based on known requirements for binding to H-2Kd (page 438, first column, lines 11-16). However, the work of Abrahms et al is concerning the binding of the peptides to the H-2KD and does not address the generation of a CD+8 immune response in vivo that is effective for immunotherapy of a tumor. Abrahams et al teach that lysis of A20 cells transfected with the mutant Ras peptides, but that A20 cells transduced with the wild type sequence of Ras were not lysed consistent with the recognition of the appropriate peptide MHC I complex for T cell recognition (page 440, second column, lines 10-15).

It is concluded based on the references discussed above, that the state of the art with respect to treating patients with cancer by means of administering tumor antigen precursors or tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs which lyse the cells of a tumor in situ, or that tumor cells in a patient would harbor the all of the variant K-ras peptides claimed. It cannot be predicted based on the lysis of a cell in vitro by a CTL specific for a single amino acid which falls within the scope of the claims that all the variant peptides claimed would induce a CTL+8 response in a human in vivo which would be effectively inhibit tumor growth. Thus, without a demonstration that the administration of the claimed polypeptides or administration of antigen-presenting cells expressing said peptide cells are effective to overcomes immunosuppression of the host, the rapid growth of the target tumor cells, failure to access the tumor because of the stromal barrier and tolerance induction in the host and objective evidence that the target tumor cells in vivo present adequate tumor rejection antigen on the surface of all the tumor cells which correspond to all species of peptide variants claimed, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed method of treatment.

7. All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

7/26/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER

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